REMARKS

Reconsideration and allowance of the subject application are respectfully requested.

Claims 9, 25 and 31-56 are pending in the application. Basis for new claim 53 can be found in the specification and pending claim 38. Basis for new claims 54-56 can be found in the present specification including at page 23, lines 3-4 and 14 of the translation. No new matter has been added.

Claim 44 has been amended to clarify that the excipient is dissolved in the liquid and the matrix material is suspended in the liquid. No new matter has been added.

On page 8 of the Office Action, the Examiner argues that the Information Disclosure Statement (IDS) filed November 13, 2002 fails to comply with CFR 1.97(d) because its lacks the fee set forth in 37 C.F.R. 1.17(p). Applicant respectfully submits that Rule 97(d) does not apply to an IDS submitted in a Request for Continued Examination (RCE). Applicant respectfully submits that the November 13, 2002 IDS should have been considered pursuant to 37 C.F.R 1.114(c) and (d), which relate to RCE practice. The November 13, 2002 IDS is considered a "submission," as stated in Rule 114(c) "[a] submission as used in this section includes ... an information disclosure statement." Rule114(d) provides "[i]f an applicant timely files a submission and fee set forth in § 1.17(e), the Office will withdraw the finality of any Office action and the submission will be entered and considered." Since Applicant timely filed the November 13, 2002 IDS submission and paid the Rule 17(e) fee, this submission must be entered and considered pursuant to Rule 114. However, if the Examiner still considers Rule 97(d) to apply to RCE practice, please charge our deposit account No. 50-0687 under order No. 62659 for the Rule 17(p) fee and consider the IDS. Applicant reserves the right to contest payment of the Rule 17(p) fee.

The rejection of claims 44-50 under 35 U.S.C. § 112, second paragraph, is obviated by the amendment to claim 44 as set forth above. Accordingly, withdrawal of

the Section 112 rejection is respectfully requested.

The rejection of claims 9, 31-35, 38, 40-46 and 50 under 35 U.S.C. § 102(e) as being anticipated over Chen is respectfully traversed. The claimed invention is not anticipated by Chen for the many reasons of record and for the following reasons.

Claims 44-46 and 50 recite the step of "dissolving the excipient in a liquid." In contrast, Chen teaches that excipient is not dissolved in the liquid, but rather suspended. The Examiner confirms such by stating "then add an amount of excipient to the solution to form a suspension" on page 4 of the Office Action. For this reason alone, the Section 102 rejection of claims 44-46 and 50 should be withdrawn.

Claims 9, 31-35 and 38 all require that the excipent phase be coherent. This is achieved by dissolving the excipient in the liquid. If the excipient is suspended in the liquid, it would form an incoherent excipient phase, which is different from the claimed invention. Since Chen teaches to suspend the excipient, as acknowledged by the Examiner, the particles of Chen must have an incoherent excipient phase, which is patentably different form the coherent excipent phase in the claimed particles. For this reason alone, the Section 102 rejection should be withdrawn.

Chen describes the dissolution of one specific drug (sodium diclofenac) in water, an excipient is added (e..g. lactose), a non-soluble polymer is dispersed (one specific Eudragit type) and the powder is spray-dried. However, this is only part of what Chen teaches. **Chen continues by saying that the spray dried product needs to be further processed to a tablet, requiring the addition of a mixture of microcristalline cellulose and starch to bind it together. See column 3, lines 11-26 of Chen. The mixture of Chen does not bind without an additional excipient and, thus, has a different structure than the claimed invention.**

In contrast to Chen, the claimed invention is directly compressible into a tablet and no further binders are required. Chen discloses the opposite of the claimed invention, indirect compression using binders. For this reason alone, Chen cannot anticipate the claimed invention.

On page 5 of the Office Action, the Examiner argues that "Chen formulates his

powder using the same components as instantly claimed, in the same concentrations via the same process steps ... Chen further shows that the microcapsule powders obtained by his method show a compressability of about 50%."

Applicant respectfully submits that Chen does not use the same components nor the same method steps. As discussed above, the claimed invention dissolves an excipient to form a coherent excipient phase and Chen suspends an excipient form and incoherent excipient phase. Furthermore, claim 50 requires that the active agent be insoluble in the liquid, whereas Chen teaches only to use soluble active agents. The powders of Chen have a very different composition and structure than the claimed powders.

Chen's powders are not directly compressible into tablets. Indeed, Chen specifically teaches that a binder is required for forming tablets, as discussed previously. The fact that Chen's powder is compressible about 50% actually teaches against being directly compressible into tablets for the following reasons.

To clarify the terminology, the process to produce tablets in a tabletting machine is either called "compression", also the term "compaction" is in use (depending on which latin word the term is derived from, either from "comprimere" (compressus) or from "compingere" (compactus)). The term compression is used in the patent application in this sense that tablets can be produced in a compression process.

The term compression is also used in general in case something reduces its dimensions or its volume (corresponding to increase its density, e.g. a powder reducing its volume by getting a denser packing under vibration).

The examiner argues that Chen's composition is compressible – in contrast to Applicant's arguments that said composition is not compressible. The examiner cites the compressibility index disclosed in Chen being 50%. However, from a compressibility index no conclusion can be made at all whether a powder is compressible to form solid comprimates, such as tablets. This index is only the ratio between bulk density of a powder and the tapping (tapped) density, the tapped density is also called compressed bulk density. According to the Encyclopedia of Pharmaceutical Technology, volume 2, J. Swarbrick and J.C. Boylan (eds.), Marcel Dekker, New York, 2002, pages 1272

and 1273: "The bulk density of a powder is obtained by dividing the mass by the bulk volume it occupies. The volume includes the spaces between the particles...." "The tapped density is the bulk density of a powder which has been compacted by tapping or vibration following a special procedure.....The sample is dropped (tapped) ..at a set frequency for a fixed number of times." For example, 100 g powder poured into a measuring cylinder, the bulk density calculated and then the cylinder tapped 1250 times, the powder reduces its volume by smaller particles moving into the spaces, the reduced volume leads a higher tapping density, tapping device after Neumann. See attached diagram of the tapping device.

To sum up, the index calculated is only a measure to which extent a powder reduces its volume by obtaining a denser packing under vibration or tapping. It does not teach anything at all regarding whether or not such powders are able to form a comprimate/tablet having a sufficient binding strength.

The present invention is characterized in that that the compounds can be directly tabletted in a direct compression procedure to form firm, solid tablets. On the contrary, the high compressibility of 50% cited by the examiner is clear proof that Chen's powders are not suitable for direct compression. In the textbooks, it is clearly stated that the difference between bulk density of a powder and tapped density should be as small as possible, ideally they should be identical, that means compressibility of the powder should be ideally 0%. If powders have a high compressibility, they will reduce their volume under the vibrations of the tabletting machine. Tablets are dosed via volume and highly compressible powders in the tapping test will increase their density during the tabletting process thus leading to dose inaccuracy. For such powders it is recommended to add excpients such as microcrystalline cellulose or to perform a granulation process (i.e. direct compresion is not possible any more without additives).

The powders of Chen show a very high compressibility of 50% and more. This is the classical situation of the textbooks for adding excipients, exactly what Chen is doing. In lines 13-15 of the abstract and col. 8, lines 39-41 (both also cited by the examiner) microcrystalline cellulose and starch are added, which are classical binders in

pharmaceutical technology. From this, the powders of Chen cannot anticipate the direct tabletting feature of the claimed invention.

Since Chen's powders use different excipients and use a different method of manufacture than the claimed powders, Chen's powder cannot inherently teach a powder being directly compressible into tablets, as alleged by the Examiner on page 5 of the Office Action. Furthermore, Chen even requires the use of binders to form tablets, as discussed above. Chen's teaching to use binders to form tablets cannot be simply ignored and surely not completely reversed to now teach to form tablets without using such binders. Those skilled in the art follow teachings in the prior art, not the reverse of those teachings.

For these reasons and the reasons of record, the claimed invention cannot be anticipated by Chen. Accordingly, withdrawal of the Section 102 rejection is respectfully requested.

The rejection of claims 9, 25, 31-43, 51 and 52 under 35 U.S.C. § 102(e) as being anticipated over Takada is respectfully traversed. The claimed invention is not anticipated by Takada for the following reasons.

Takada prepares polymeric microparticles containg a drug, where an aggregation preventing agent (e.g. mannitol) is sprayed on the surface of the mircoparticles. Takada's microparticles are different than the formulation of the present invention.

The compounds of the invention are characterized in that the drug-containing compound particles are composed of drug-free insoluble polymer particles and the drug, when present, is located between the polymeric particles-not inside a microparticle. See Figure 4 lower right of the present patent application. In contrast, in Takada a microparticle of drug/polymer is formed and then coated with the aggregation preventing agent.

Since the claimed formulation has a different structure than Takada, the claimed formulation can be directly compressed to form tablets, i.e. without the use of binders. In contrast, the microparticles of Takada require the use of binders to form tablets. See column 9, line 59 of Takada.

In addition, the process of forming the microparticles according to Takada is different from the processes for forming the claimed formulations:

1. Takada prepares o/w droplets (e.g. acetonitrile in water, example 4) or multiple w/o/w droplets (example 1) which are formed in the spray dryer. In each case the polymer is dissolved in an organic liquid. In contrast, in the present invention a pre-requisite is that the polymer is insoluble in the spraying mixture, i.e. it is a polymer suspension.
2. Takada sprays emulsions of different types (simple, multiple), whereas the invention is only spraying suspensions.
3. A pre-requisite of Takada is the use of a two-fluid nozzle to form the microparticles and then coat the microparticles. In contrast to this, the present invention cannot use a two-fluid nozzle since a single suspension is formed.

In summary, a process being different in the apparatus used (two- vs. one-fluid nozzle) and being different in the physical form of the sprayed compounds (dissolved polymer in emulsion vs. insoluble polymer suspensions) will lead to a different product. According to Takada the drug is inside the polymer particles, and according to the present invention outside the polymer particles.

In view of the many differences between the claimed invention and Takada, the Section 102 rejection should be withdrawn.

The rejection of claims 31-40 and 43-50 under 35 U.S.C. § 103 over JP '518 is respectfully traversed. Claims 31-40 and 43-50 are not taught or suggested by JP '518 for the following reasons.

JP '518 describes a traditional spray-drying process to convert a drug with less suitable size distribution (broad distribution, polydisperse) to a particle powder of uniform size. Uniform powders show better flow properties than polydispersed ones (e.g. typical examples are uniformly sized corn starch particles having distinctly better flow properties compared to the larger sized and polydisperse potato starch). Consequently, JP '518 states that the obtained compound has improved flowability (the word "fluidity" used in the translation is an incorrect translation from the Chinese original). Because it flows better, it has an improved miscibility with other excipients, this mixture then

being more suitable for direct tabletting compared to a polydisperse one (general textbook knowledge). From this - better flowability - it cannot be concluded even deduced that the produced particles themselves have the special property of the present invention of enabling direct compression without further binders.

Many powders have good flowability (one of the many pre-requisites for direct tabletting), but flowability does not automatically include the ability to form a firm comprimate. For example Aeroperl (a product from Degussa, particulate siliciumdioxide) flows perfectly, but forms no solid comprimates when used on its own without binders. Even when adding 30% of Emcompress - a very efficient binder - no firm tablets can be obtained. Emcompress is calcium salt binder product by the American company Penwest.

In summary, good flowability provides no evidence for compressability to form a tablet.

JP '518 states that the drug suspension to be spray-dried can (not must) contain other agents such as water-soluble polymers/macromolecules, soluble cellulose derivatives, insoluble cellulose derivatives, starch, lactose etc. It is more or less an extensive list of standard excipients used in spray-drying. There is no teaching at all that the obtained product has good compactability properties (only a good flow). Furthermore, it is described that it can be used as a raw material (not a ready-to-use mixture) for direct tabletting. In addition there is no teaching that a firm combination of drug, polymer and water soluble excipient needs to be used. Especially no hint, that the polymer needs to be insoluble in the spray-drying mixture whereas the excipient needs to be soluble.

The list of agents disclosed in JP '518 corresponds to the list of standard additives from textbooks given as additives in a general spray-drying process. Because of this, JP '518 in fact teaches away from the from the present invention when soluble polymers such as PVP are recommended or water insoluble non-polymeric excipients such as starch are recommended. The teaching also emphasizes that for compression to tablets microcrystalline cellulose or other additives such as starch have to be added. From this, one of ordinary skill in the art would not assume or consider it as possible that a mixture

could be developed which itself has direct compression properties, i.e. that no compression additives (binders) are required to form tablets.

The present invention thus exhibits the unexpected property of being directly compressible into firm tablets without the use of binders.

Applicant respectfully submits that the Examiner's argument on page 7 of the Office Action that "it would be obvious to one of ordinary skill in the art at the time of the invention to add any such components to the suspension of folic acid during the process and prior to spray drying step and formulate the powders containing a polymer, or a cellulose derivative in combination wit lactose for their known intended use, because as suggested by JP '518, such ingredients may be utilized and the ordinary skill in the art would have had a reasonable expectation of success in using them," is without merit. The prior art, including JP '518, does not teach or even suggest a method of making a formulation that can be directly compressed into tablets. Indeed, the prior art in fact teaches to form compositions that require binders for forming tablets. The Examiner has cited no teaching for directly forming tablets from a formulation without the use of binders.

In view of the many differences between the claimed invention and JP '518 and the unexpected advantages of the claimed invention, withdrawal of the Section 103 rejection is respectfully requested.

The rejection of claims 9, 25, and 31-52 under 35 U.S.C. § 103 over JP '518 in view of Takada is respectfully traversed. Claims 9, 25 and 31-52 are not taught or suggested by Takada for the many reasons provided above and JP '518 does not provide the deficiencies of Takada.

Neither of Takada or JP '518 teach or even suggest a formulation or method of making a formulation which can be directly compressed into tablets without the use of binders. Indeed, Takada teaches against such by requiring the use of binders, as discussed above. JP '518 teaches a folic acid formulation for use as "a raw material for direct tableting of tablet" which means that that formulation must be mixed with binders to form a tablet as is conventional in the prior art. The Examiner admits that the formulation

of JP '518 is different from the claimed formulation. The combination of these references clearly teaches formulations that require the use of binders.

In view of the many differences between the claimed invention and JP '518 and the unexpected advantages of the claimed invention, withdrawal of the Section 103 rejection is respectfully requested.

In view of all of the objections and rejections of record having been addressed, it is believed that the present application is in condition for allowance and Notice to that effect is respectfully requested.

Respectfully submitted,

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